ISIS-4789 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Manoharan et al.

Serial No.: Not Yet Assigned

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For:

OLIGONUCLEOTIDES HAVING A-DNA FORM AND B-DNA FORM

CONFORMATIONAL GEOMETRY

EXPRESS LABEL NO. EL650276764US DATE OF DEPOSIT: October 4, 2001

Assistant Commissioner for Patents Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination of the above-captioned patent application, Applicants respectfully request entry of the following amendments, without prejudice:

In the Claims

Please cancel claims 14-17, 19-20 and 33-36, without prejudice, and amend claims 1 and 4 as follows:

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1. (Amended) An oligonucleotide comprising a plurality of nucleotides, wherein:

a first portion of said plurality of nucleotides have B-form conformational geometry and are joined together in a continuous sequence, at least two of said nucleotides of said first portion being ribonucleotides; and

a further portion of said plurality of nucleotides are ribonucleotide that have Aform conformation geometry and are joined together in at least one continuous sequence.

4 (Amended). The oligonucleotide of claim 1 wherein each nucleotide of said further portion, independently, is a 2'-fluoro nucleotide or a nucleotide having a 2'-substituent having the formula I or II:

wherein

E is C_1 - C_{10} alkyl, $N(Q_1)(Q_2)$ or $N=C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1 - C_{10} alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support, or Q_1 and Q_2 , together, are joined in a nitrogen protecting group or a ring structure optionally containing at least one additional heteroatom selected from N and O;

 R_3 is OX, SX, or $N(X)_2$;

each X is, independently, H, C₁-C₈ alkyl, C₁-C₈ haloalkyl, C(=NH)N(H)Z,

C(=O)N(H)Z or OC(=O)N(H)Z;

Z is H or C₁-C₈ alkyl;

 L_1 , L_2 and L_3 form a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;